Dyskinesia and Parkinsonism in Antipsychotic-Naive Patients With Schizophrenia, First-Degree Relatives and Healthy Controls: A Meta-analysis

Jeroen PF Koning[1–3]**, Diederik E. Tenback**[2,4]**,
Jim van Os**[5,6]**, André Aleman**[7,8]**, René S. Kahn**[3,4]**, and
Peter N. van Harten**[2,8]

[2]Psychiatric Center Symfora groep, Amersfoort, The Netherlands;
[3]Rudolph Magnus Institute of Neuroscience; [4]Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands; [5]Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, The Netherlands; [6]Division of Psychological Medicine, Institute of Psychiatry, London, UK; [7]BCN Neuroimaging Center; [8]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Background: Several studies have reported the presence of dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia as well as in their first-degree relatives. These movement disorders may therefore form an integral part of the illness and its (genetic) liability. *Method:* A systematic search was conducted in the Medline, EMBASE, and PsychINFO databases to identify studies reporting on dyskinesia and parkinsonism assessed in antipsychotic-naive patients with schizophrenia ($n = 213$) and controls ($n = 242$) and separately in nonill first-degree relatives ($n = 395$) and controls ($n = 379$). Effect sizes were pooled using random-effect models to calculate odds ratios (ORs) to compare the risk of these movement disorders among patients and healthy relatives each with matched controls. *Results:* Antipsychotic-naive schizophrenia was found to be strongly associated with dyskinesia (OR: 3.59, 95% confidence interval [CI]: 1.53–8.41) and parkinsonism (OR: 5.32, 95% CI: 1.75–16.23) compared with controls. Dyskinesia and parkinsonism were also significantly more prevalent in healthy first-degree relatives of patients with schizophrenia as compared with healthy controls (OR: 1.38, 95% CI: 1.06–1.81, and OR: 1.37, 95% CI: 1.05–1.79, respectively). *Conclusion:* The results suggest that movement disorders, and by inference abnormalities in the nigrostriatal pathway, are not only associated with schizophrenia itself but may also be related to the (genetic) risk of developing the disease.

[1]To whom correspondence should be addressed; c/o. Mrs T. van Polanen, Symfora groep, Medisch centrum, PO Box 3051, 3800 DB Amersfoort, The Netherlands; tel: +31-33-4609568, fax: +31-33-4609557, e-mail: jpf.koning@symfora.nl.

Introduction

Movement disorders such as dyskinesia and parkinsonism are primarily associated with the use of antipsychotic medication, particularly in patients with schizophrenia.[1–3] However, involuntary hyper- and hypokinetic movements have been described in patients with schizophrenia long before the introduction of antipsychotic medication.[4–6] This suggests that these abnormal movements may be related to the illness itself rather than just the result of antipsychotic medication. If abnormal movements were related to the disease, one would expect these movement disorders to be present in antipsychotic-naive patients with schizophrenia. However, although numerous studies[7–28] examined the presence of these abnormal movements in antipsychotic-naive patients with schizophrenia, only a few have compared the prevalence of these signs with that in a matched healthy control group.[7,8,11,12,15,21,24] Interestingly, while the uncontrolled studies (mostly) observed movement disorders in antipsychotic-naive patients,[9,10,13,14,16–20,23,25–28] the controlled studies generally did not report significantly more movement disorders in patients than in healthy controls.[7,8,11,12,15,24] If dyskinesia and parkinsonism are present in first-degree relatives of patients with schizophrenia, these movement disorders may be related to the (genetic) risk of developing the disease. However, studies comparing the presence of dyskinesia and parkinsonism in healthy relatives and controls[21,29–36] generally report inconclusive results.
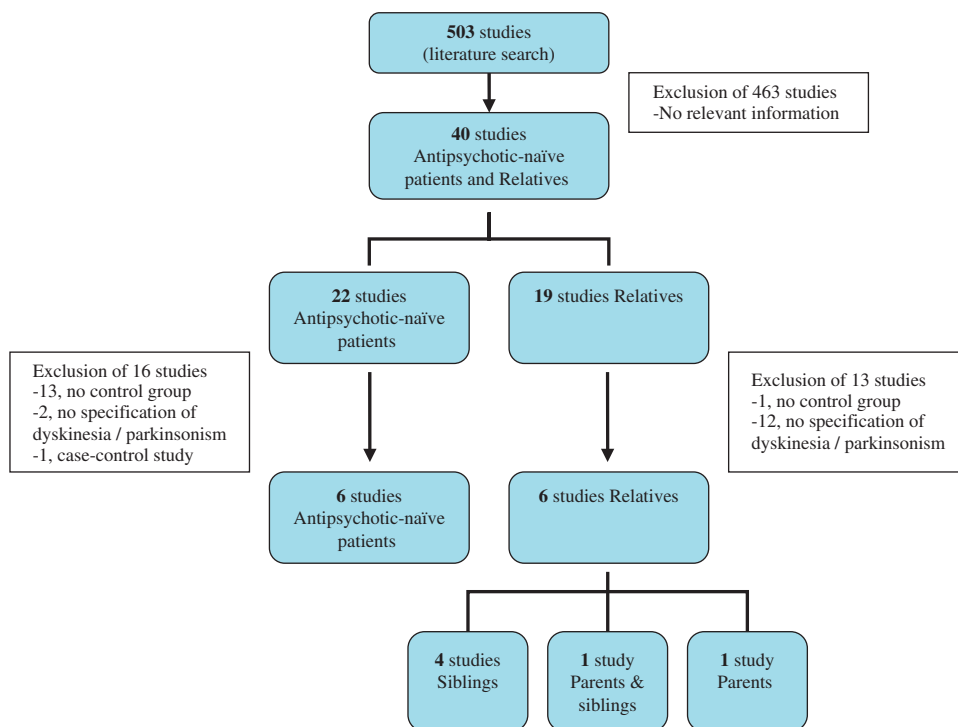
Therefore, we conducted a meta-analysis to systematically compare the prevalences of dyskinesia and parkinsonism in schizophrenia patients and healthy first-degree relatives each with age-matched controls in the same study.

Methods

Data Sources

The registers of Medline, EMBASE, and PsychINFO were searched without year limits up to January 2008

Fig. 1. Flowchart of Included Studies.

using the following keywords: (dyskinesia or parkinsonism or movement disorders) combined with (antipsychotic-naive or treatment-naive or naive and schizophrenia) and separately with (relatives or family members or parents or offspring or children or siblings and schizophrenia). In addition, all relevant references cited in the articles found were also retrieved. This yielded 503 results, of which 40 original studies contained relevant information. As listed in figure 1, of these 40 studies, 12 were included according to our inclusion criteria: (1) examined dyskinesia and/or parkinsonism in antipsychotic-naive patients with schizophrenia or in their healthy first-degree relatives, (2) compared the results with a healthy control group matched for age, and (3) reported sufficient data to obtain an effect size as measured by prevalences or mean scores, SDs, and number of subjects in each group. Of the 29 excluded studies, 16 studies were on antipsychotic-naive patients[9,10,13,14,16,17,19,20,22,23,25–28,37,38] of which 13 had no control group,[9,10,13,14,16,17,19,20,23,25–28] 1 study was a case-control study,[22] and 2 studies did not specify for dyskinesia or parkinsonism.[37,38] Of the remaining 13 excluded studies on healthy relatives[32,34,35,39–48] (7 on offspring,[39,40,42–45,47] 4 on parents and siblings,[32,34,35,46] 1 on siblings,[48] and 1 on first- and second-degree relatives[41]), 12 studies did not specify for dyskinesia or parkinsonism,[32,34,35,39,40,42–48] and 1 did not include a control group.[41] We had access to the original data of 1 study,[29] and 1 author was contacted and provided the information on dyskinesia in the patient

and control group, which data was not clearly presented in the published manuscript.[7]

Statistical Methods

Effects were pooled calculating the odds ratio (OR) comparing the risk of dyskinesia and/or parkinsonism of patients and first-degree relatives, each with age-matched healthy controls. The presence of dyskinesia in studies on patients and matched controls was defined by a score of 2 or greater on one item on the Abnormal Involuntary Movement Scale (AIMS)[49] or on the Extrapyramidal Symptoms Rating Scale (ESRS-IV) dyskinesia.[50] Presence of parkinsonism in patient studies was defined by a total mean score of at least 0.3 on the Simpson Angus Scale (SAS), which is a 10-item scale that has been validated and used widely for the assessment of neuroleptic-induced parkinsonism in both clinical practice and research setting.[51] If the included studies used less stringent cutoff points and the result sections of those studies provided sufficient information, the results were adjusted using the mentioned research criteria for tardive dyskinesia[7,25,52] and parkinsonism.[12,16] The prevalences of dyskinesia in 2 studies[7,12] and of parkinsonism in 1 study[8] could be adjusted according to the cutoff criteria because sufficient detailed information was reported in the "Results" section. Of 1 study, we received information from the author.[7]

In case of cell frequencies equal zero using ORs, 0.5 was added to the cell frequencies to solve this problem by eliminating any zeros but creating a downward

Table 1. Characteristics and Prevalences of Dyskinesia and Parkinsonism in Antipsychotic-Naive Patients With Schizophrenia[a] and Healthy Controls

Study	N, Patient/Control	Mean Age (y), Patient/Control	Males (%), Patient/Control	Mean Duration Illness (y)	Country	Dyskinesia (%), Patient/Control	Parkinsonism (%), Patient/Control
Chorfi (1989)	50/50	24/24	88/NR	1/—	Morocco	0/0[b]	—/—
Cortese (2005)	39/25	24/24	82/56	First episode	Canada	5/0[c]	18/0[d]
Hoffman et al[15] and Moussaoui et al[24]	62/21	30/29	NR	6/—	Morocco	26/0[e]	—/—
Caligiuri and Lohr[7]	17/21	37/37	100/100	6/—	United States	6/0[b]	—/—
Caligiuri et al[8]	24/24	42/42	83/NR	5/—	United States	—/—	4/0[d]
McCreadie et al[21]	21/101	65/63	43/47	14/—	India	38/15[e]	24/6[d]

[a]100% *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*, or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria.
[b]Abnormal Involuntary Movement Scale (AIMS), item score $\geq$ 2 (research criteria).
[c]Extrapyramidal Symptoms Scale (ESRS-IV), item score $\geq$ 2.
[d]Simpson Angus Scale (SAS), mean score of at least 0.3.
[e]AIMS, item score $\geq$ 3 or on 2 items score $\geq$ 2 (Schooler and Kane crieria[72]).
Not Reported (NR)

bias and slightly understating the strength of the relationship.[53,54]

The prevalences of dyskinesia and parkinsonism in studies on first-degree relatives were presented as mean scores, which were used to calculate Cohen *d* (a standardized mean difference effect size) that could be converted into ORs with the use of formula 1.[55] Formula 1: $ES_{or} = e^{(\pi \times ES/\sqrt{3})}$

In this formula, ES_{or} is the OR equivalent from the continuous dependent measure, ES = effect size, π = 3.14, and e = natural logarithm.

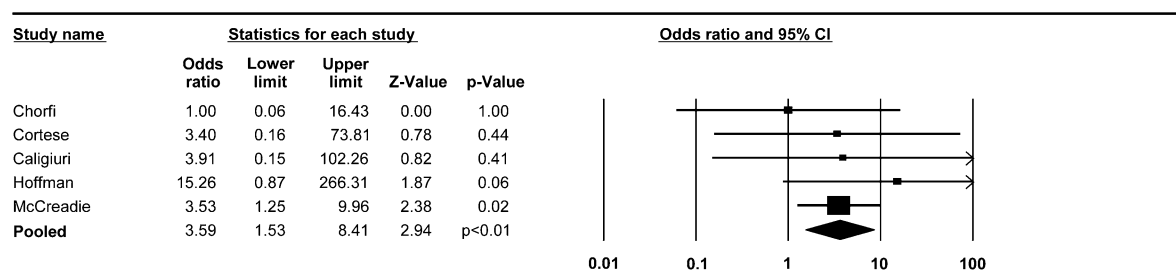The following measures or items from the different studies represent dyskinesia in the pooled analysis: AIMS[21]; modified AIMS[31]; involuntary movements from the Woods Scale (including choreiform and athetotiform movements)[56]; limb and orofacial dyskinesia items from the Cambridge Neurological Inventory[30]; chorea, athetosis, choreoathetosis, akathisia in accordance with the textbook definitions[36,57]; and choreiform movements (from the Woods Scale).[29] For parkinsonism, the components included were SAS,[21] modified AIMS including parkinsonian signs,[31] involuntary movements from the Woods Scale (including postural, intentional/resting tremor),[33] glabellar sign, increased limb tone, decreased associated movements in walking, shuffling gait, arm dropping test, tremor and neck rigidity from the Cambridge Neurological Inventory,[30] resting tremor in accordance with the textbook definition,[36,57] cogwheel rigidity, parkinson gait, and resting tremor (from the Woods Scale).[29]Because the distribution of the mean prevalence scores in siblings and controls were skewed, this might invalidate the results as Cohen *d* assumes normality.[58] We therefore combined the probabilities from the independent studies for which a *Z* value could be calcu-

lated[21,29–31,36] to test whether there might be sufficient evidence to reject the null hypothesis.[59] Weighting of the studies was according to their power.

Meta-regression analysis was used to investigate the impact of continuous study moderators on overall heterogeneity. The regression models were estimated by unrestricted maximum likelihood. For the prevalences of dyskinesia and parkinsonism, the following moderators were tested: mean age of patient, mean age at onset, mean duration of untreated illness, and sex. To examine the statistical heterogeneity of the individual studies, we tested a homogeneity statistic, *Q*. Additionally, to examine the possibility of publication bias, a method to indicate the number of unpublished studies with null effects that must reside in file drawers to reduce the observable effect size to a negligible level, we used the fail safe number according to Orwin.[54,60] The threshold criterion for a negligible level was set at an OR of 1.2. All analyses were carried out in the random-effects model using the Comprehensive Meta-Analysis package (www.meta-analysis.com).

Results

Table 1 lists the characteristics of the studies on antipsychotic-naive patients with schizophrenia. As presented in figure 2, the results of our meta-analysis indicate that dyskinesia is strongly associated with schizophrenia with an OR of 3.59 ($P < .01$). This analysis included 5 studies with a group size of 189 patients with schizophrenia and 218 controls. Excluding the study[21] that contributed most to the effect would reduce the significance level into a trend (OR = 3.72, $P = .08$). As presented in figure 3, the OR for an association with parkinsonism was 5.32 ($P < .01$). The analysis of parkinsonism included 3 studies, with a group

Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Chorfi	1.00	0.06	16.43	0.00	1.00	
Cortese	3.40	0.16	73.81	0.78	0.44	
Caligiuri	3.91	0.15	102.26	0.82	0.41	
Hoffman	15.26	0.87	266.31	1.87	0.06	
McCreadie	3.53	1.25	9.96	2.38	0.02	
Pooled	3.59	1.53	8.41	2.94	p<0.01	

Fig. 2. Forest Plot and Odds Ratios of Dyskinesia in Antipsychotic-Naive Patients With Schizophrenia Compared With Healthy Controls.

size of 84 patients with schizophrenia and 150 controls. If we excluded the study that contributed most to the effect,[21] the significance level would be reduced to a trend; OR = 6.53 ($P = .09$).

An increase in the prevalence of dyskinesia with increasing age was significant and similar in both patients and controls ($\beta = .07$, $P = .02$, and $\beta = .06$, $P < .01$). In addition, the prevalence of dyskinesia increased significantly with duration of untreated schizophrenia ($\beta = .28$, $P < .01$). There was no significant correlation with age at onset of schizophrenia ($\beta = .15$, $P = .07$). However, age, duration of untreated schizophrenia, and age at onset were significantly correlated with each other ($r > 0.85$, $P < .05$). For parkinsonism, no significant increase in prevalence was observed in either the patients or controls with regard to age ($\beta = .01$, $P = .44$, and $\beta = .03$, $P = .27$, respectively), duration of untreated schizophrenia ($\beta = .04$, $P = .43$), or age at onset ($\beta = .01$, $P = .82$). Gender differences could not be calculated because only one study provided information on gender distribution in the result section.[21]
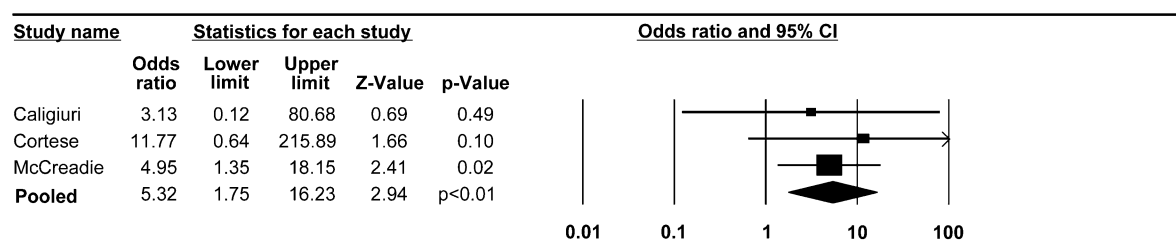
Table 2 contains information regarding studies of dyskinesia and parkinsonism in first-degree relatives of patients with schizophrenia. Six studies evaluated dyskinesia and parkinsonism including 395 siblings and 379 healthy controls, of which 4 were on siblings,[30,31,33,36] 1 on parents and siblings,[21] and 1 on parents.[29] The meta-analysis indicates small but significant differences when the prevalences of dyskinesia and parkinsonism in first-degree relatives were compared with healthy control subjects (figures 4 and 5), with a mean weighted OR of 1.38 (95% CI: 1.06–1.81) and z value of 2.28 ($P = .02$) for dyskinesia and an OR of 1.37 (95% CI: 1.05–1.79) and z value of 2.21 ($P = .03$) for parkinsonism.

Heterogeneity and Publication Bias

No significant heterogeneity was apparent for the dyskinesia and parkinsonism analyses in patients vs controls ($Q = 1.79$, $P = .77$, and $Q = 0.40$, $P = .82$) or in siblings vs controls ($Q = 0.73$, $P = .98$, and $Q = 2.30$, $P = .81$). The fail-safe number was large enough to provide credence to our findings for the dyskinesia and parkinsonism analyses in patients vs controls (30 and 25) but suggested that the possibility of publication bias warrants a cautious interpretation of the results for siblings vs controls (5 and 5 studies, which is almost equal to the number of published studies).

Discussion

This meta-analysis about dyskinesia and parkinsonism integrated the results of 6 studies in antipsychotic-naive patients ($n = 213$) with schizophrenia and healthy controls ($n = 242$) and separately the results of 6 studies in first-degree relatives ($n = 395$) and healthy control subjects ($n = 379$). We found schizophrenia to be strongly associated with dyskinesia and parkinsonism. Because we only included studies regarding antipsychotic-naive patients, these findings suggest that these movement disorders are related to schizophrenia itself and cannot be explained on the basis of the use of antipsychotic medication. Interestingly, these results are consistent with reports of similar motor symptoms in schizophrenia patients in the preneuroleptic era[4–6] and with results of recent publications on neuroleptic-naive patients and relatives using more liberal inclusion criteria.[61–63] Age and duration of illness correlated positively with the prevalence of dyskinesia, but because the correlation between age and duration of illness (and age of illness

Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Caligiuri	3.13	0.12	80.68	0.69	0.49	
Cortese	11.77	0.64	215.89	1.66	0.10	
McCreadie	4.95	1.35	18.15	2.41	0.02	
Pooled	5.32	1.75	16.23	2.94	p<0.01	

Fig. 3. Forest Plot and Odds Ratios of Parkinsonism in Antipsychotic-Naive Patients With Schizophrenia Compared With Healthy Controls.

Table 2. Characteristics and Mean Scores of Dyskinesia and Parkinsonism in Healthy First-Degree Relatives of Patients With Schizophrenia and Healthy Controls

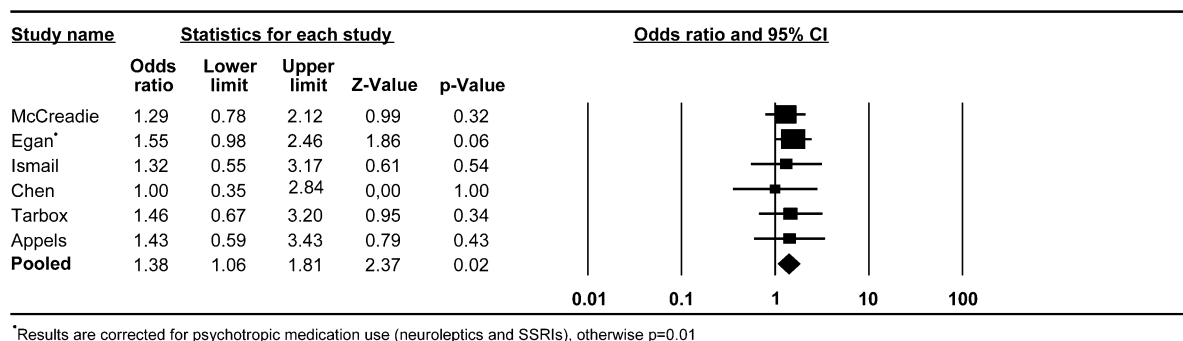| Study	N, Relative/Control	Mean Age (y), Relative/Control	Males (%), Relative/Control	Country	Dyskinesia (Mean Score), Relative/Control	Parkinsonism (Mean Score), Relative/Control
Chen et al[30] (siblings)	21/26	31/31	29/42	Hong Kong	0.0/0.0	0.10/0.0
Tarbox and Pogue-Geile[36] (siblings)	33/55	31/29	39/42	USA	286/216	0.3/0.0
Egan et al[31] (siblings)	185/88	36/33	43/42	USA	1.15/0.75	0.58/0.19
Ismail et al[33] (siblings)	21/75	38/36	73/79	Sweden	0.19/0.02	0.19/0.02
McCreadie et al[21] (parents and siblings)	103/101	63/63	48/47	India	0.55/0.43	11%/6%[a]
Appels et al[29] (parents)	32/34	55/55	50/50	Netherlands	0.63/0.4	0.03/0.06

[a]No mean scores were given, only percentages of Simpson Angus Scale mean scores of at least 0.3 (see ''Methods'' section).
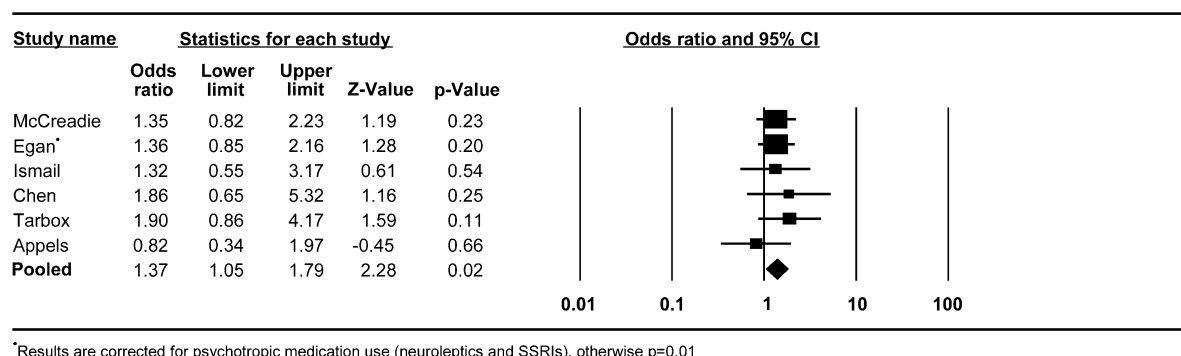
onset) itself was very high ($r > 0.85$), it was not possible to discriminate reliable between these factors using multivariate meta-regression analysis due to this multicollinearity. However, because we found no difference between patients and controls on the effect of age on the prevalence, age is most likely a general risk factor for dyskinesia. Additionally, gender differences could not be calculated because only one study provided information on gender distribution in the ''Results'' section.[21] Dyskinesia and parkinsonism were also more prevalent in healthy first-degree relatives of patients with schizophrenia compared with controls. The differences were small but significant, suggesting that these movement disorders might also be related to the (genetic) risk of developing schizophrenia. One possible mechanism for a common (genetic) vulnerability for movement disorders and schizophrenia may be an increased presynaptic dopamine activity and/or sensitivity in the nigrostriatal pathway. Imaging studies have not only shown an increased accumulation of labeled dopamine in the striata of unmedicated patients with schizophrenia[64,65] but also in healthy first-degree relatives (children and siblings) of patients with schizophrenia.[66] It has indeed been suggested that in schizophrenia, striatal dysfunction initially manifests itself in the form of movement disorders and gradually leads to prodromal and eventually to psychotic symptoms as the striatal circuitry matures during adolescence.[67–69]

Some limitations in this meta-analysis should be noted. First, there was diversity in items and scales used to evaluate dyskinesia and parkinsonism. The adjustments of the diagnostic criteria for dyskinesia and parkinsonism have been thought to facilitate the differences among the studies. In addition, the use of pooled ORs as a measure of standardized mean difference should produce results independent of scale and range. Second, the inclusion criteria were limited to studies reporting on dyskinesia and parkinsonism. Therefore, prevalence numbers of other motor abnormalities including neurological soft signs, such as motor coordination and imbalance, are excluded (for a review, see Wolff and O'Driscoll[61]). However, by focusing on dyskinesia and parkinsonism that are rather specific for schizophrenia contrary to soft neurological signs that are also seen in mood disorders,[70] the strength of the relationship between hard neurological signs and schizophrenia could be estimated.

Third, the duration of untreated psychosis (DUP) can be a confounder because longer duration of illness may

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
McCreadie	1.29	0.78	2.12	0.99	0.32
Egan*	1.55	0.98	2.46	1.86	0.06
Ismail	1.32	0.55	3.17	0.61	0.54
Chen	1.00	0.35	2.84	0,00	1.00
Tarbox	1.46	0.67	3.20	0.95	0.34
Appels	1.43	0.59	3.43	0.79	0.43
Pooled	1.38	1.06	1.81	2.37	0.02

Odds ratio and 95% CI

0.01   0.1   1   10   100

*Results are corrected for psychotropic medication use (neuroleptics and SSRIs), otherwise p=0.01

Fig. 4. Forest Plot and Odds Ratios of Dyskinesia in Healthy First-Degree Relatives of Patients With Schizophrenia compared with Healthy Controls.

Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
McCreadie	1.35	0.82	2.23	1.19	0.23	
Egan[*]	1.36	0.85	2.16	1.28	0.20	
Ismail	1.32	0.55	3.17	0.61	0.54	
Chen	1.86	0.65	5.32	1.16	0.25	
Tarbox	1.90	0.86	4.17	1.59	0.11	
Appels	0.82	0.34	1.97	-0.45	0.66	
Pooled	**1.37**	**1.05**	**1.79**	**2.28**	**0.02**	

[*]Results are corrected for psychotropic medication use (neuroleptics and SSRIs), otherwise p=0.01

Fig. 5. Forest Plot and Odds Ratios of Parkinsonism in Healthy First-Degree Relatives of Patients With Schizophrenia and in Healthy Controls.

increase the risk of dyskinesia and parkinsonism. In this meta-analysis, one study from Asia[21] had the largest DUP, and indeed, this study contributed the largest effect on the difference in prevalence of dyskinesia and parkinsonism between patients and controls. Fourth, a methodological problem in meta-analysis is the variance between the studies in the way the movement disorders are assessed and differentiated from other syndromes. This is particularly a problem for the symptom bradykinesia, which can not only resemble parkinsonism but also negative symptoms in schizophrenia and other disorders. However, the included studies used the SAS instrument, which items measure mainly rigidity and tremor, which are specific symptoms of parkinsonism. A recent study suggested that the mean cutoff score for the SAS of 0.3 is probably too low[71] resulting in a lower specificity. However, the cutoff point of 0.3 has been validated[51] and is widely accepted in the research of drug-induced movement disorders. In this meta-analysis, the frequently applied research criteria (score ≥ 2 on the AIMS or ESRS-IV) are used for the screening of dyskinesia. A more stringent criterion such as the Schooler and Kane criteria[72] would underestimate the prevalence. Moreover, prospective studies show that patients with dyskinesia based on the less stringent criteria as used in this meta-analysis will later meet the Schooler and Kane criteria.[52,72] Fifth, it was not possible to differentiate between dyskinesia and parkinsonism in one study[33] because the involuntary movements subscale included items of both movement disorders (postural/intentional/resting tremors and choreiform and athetotiform movements). Because both movement disorders reflect nigrostriatal dysfunction, the results were incorporated in both analyses (figures 4 and 5). This again resulted in an underestimation of the effect because the effect size was very small and insignificant. Excluding that study from the meta-analysis would not have influenced the results. Sixth, one study with healthy parents was included in the meta-analysis on first-degree relatives. Because parents have less risk on developing schizophrenia than siblings, this may have somewhat underestimated

the effect. Seventh, the assessments of dyskinesia and parkinsonism in siblings were not all conducted blind to the participant's group status, which could bias results. However, excluding studies in which the raters were not blind to subjects, status[30,56] would not have influenced the results significantly. Eighth, the skewness of the distributions of the mean scores of the siblings groups could be an issue because Cohen d assumes normality.[58] Therefore, an additional weighted Z method was used, validating the statistical differences between the sibling and control groups gained by the meta-analysis. It would be more ideal to restrict to psychotropic-naive patients and relatives to strengthen our conclusion. However, antipsychotics are by far the most frequent cause of drug-induced movement disorders. Moreover, only one study including antipsychotic-naive patients reported about the specific absence of other medication.[21] Of the 6 studies on relatives, 5 screened systematically for psychopathology and excluded those with a positive psychiatric history,[29–31,33,36] minimizing the chance of any other psychotropic medication use. Finally, only a proportion of the patients with schizophrenia demonstrated movement disorders and the differences between siblings and controls were small, though significant. Underestimation of the true prevalence of movement disorders might be one explanation for this finding because even trained raters, utilizing standard rating scales, have proven to be less sensitive to subclinical dyskinesia and parkinsonism than mechanical assessment.[73] Also, schizophrenia is probably heterogeneous with regard to etiology and pathophysiology[74,75]; therefore, patients with distinct nigrostriatal dysfunction may constitute a subgroup in schizophrenia.

The finding of higher rates of dyskinesia and parkinsonism in this meta-analysis is clinically relevant because the presence of these movement disorders at baseline have predicted poorer outcome of schizophrenia.[9,76,77] Future research should examine whether dyskinesia and parkinsonism constitute useful endophenotypes[78] and apply to the following criteria; the endophenotype is (1) associated with the illness in the population, (2)

heritable, (3) primarily state independent, (4) within families, co-segregating with the illness, and (5) found in affected family members is found in non-affected family members at a higher rate than in the general population the general population. The results of the current meta-analysis are in line with the first and fifth criteria. The third criterion is evidenced by a longitudinal study.[23] Therefore, extended family studies are needed to estimate the heritability and co-segregation of these movement disorders in schizophrenia. As the results of this meta-analysis show that the effects in first-degree relatives are small, future research may benefit from instrumental measurement.

In conclusion, the current results suggest that movement disorders, and by inference abnormalities in the nigrostriatal pathway are not only associated with schizophrenia itself but may also be related to the (genetic) risk of developing the disease. Moreover, research focusing on the use of symptoms of dyskinesia and parkinsonism as early predictors for schizophrenia may be warranted.

Acknowledgments

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